UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: 17-DEC-14

SUBJECT: Propamacarb hydrochloride; Review and generation of a Data Evaluation Record

PC Code: 119302
Decision No.: 495062
Petition No.: 119302-1292
Risk Assessment Type: NA
TXR No.: 0057086
MRID No.: 49452701

DP Barcode: D422720
Registration No.: NA
Regulatory Action: NA
Case No.: NA
CAS No.: 25606-41-1
40 CFR: §180.499

Ver.Apr. 2010

FROM: Anwar Y. Dunbar, Ph.D.
Pharmacologist, Risk Assessment Branch 1
Health Effects Division (HED) (7509P)

THROUGH: Charles W. Smith III,
Chief, Risk Assessment Branch 1
Health Effects Division (HED) (7509P)

TO: Christina Scheltema, Risk Review Manager
Registration Division (7505P)

I. CONCLUSIONS

RAB1 has reviewed the 28-day inhalation exposure toxicity study and it is acceptable/non-guideline studies.

II. ACTION REQUESTED

Please review this 28-day inhalation exposure toxicity study in rodents.

EPA Primary Reviewer: Hannah Pope-Varsalona, PhD **Signature:**
Risk Assessment Branch IV, Health Effects Division (7509P) **Date:** 12/17/14
EPA Secondary Reviewer: Anwar Y. Dunbar, PhD **Signature:**
Risk Assessment Branch I, Health Effects Division (7509P) **Date:** 12-18-14

Template version 09/11

TXR# 0057086

DATA EVALUATION RECORD

STUDY TYPE: Subchronic (28-day) Inhalation Toxicity - Rat; OPPTS 870.3465 [§82-4]; OECD 413.

PC CODE: 119302 **DP BARCODE:** 422720

TEST MATERIAL (PURITY): Propamocarb-hydrochloride (70.1% a.i.)

SYNONYMS: propyl *N*-[3-(dimethylamino) propyl] carbamate hydrochloride

CITATION: Weinberg, J.T. (2014). Propamocarb Hydrochloride Technical: 28-Day Inhalation Toxicity Study in Sprague Dawley Rats. Bayer CropScience AG 40789 Monheim, Germany and Agriphar S.A. 4102 Ougree, Belgium. Laboratory report number WIL-21215. May 5, 2014. MRID 49452701. Unpublished. 656 pg.

SPONSOR: Bayer CropScience AG, 40789 Monheim, Germany and Agriphar S.A., Rue de Renory 26, Bte 1, 4102 Ougree, Belgium

EXECUTIVE SUMMARY:

In a 28-day (subchronic) inhalation toxicity study (MRID 49452701), propamocarb hydrochloride (70.1% a.i., Batch No. EK1C000648) was administered to groups of 7 week old Sprague-Dawley rats (10 rats/sex/concentration) by dynamic nose-only exposure at target exposure concentrations of 0 (filtered air control), 100, 500, 1000 mg/m^3 (equivalent to analytical concentrations of 0, 0.1, 0.5, 1.0 mg/L, respectively) for 6 hours/day, 5 days/week, for 4 weeks (20 exposures for each animal). The effects and results in this subchronic inhalation toxicity study are as follows:

All animals survived to the scheduled necropsy. There were no treatment related effects on the lung or the nasal passage at any dose tested. There were no treatment-related effects on body weight for either sex, at any dose. At 100 mg/m^3, there were numerous changes in hematological and clinical chemical parameters observed in the absence of clinical signs, organ weight changes, macro- or microscopic changes, which showed no dose response, and were thus considered adaptive. Throughout the study at all doses, some hematological parameters fell outside of the registrant's historical control range.

At 500 mg/m^3, clinical examinations found facial scabbing and red material around the nose in one male starting on study Day 17 and continuing until study termination. Two males were noted with facial scabbing and red material around the nose on study Day 25 only. On Day five, one female experienced labored respiration at 1-hour post-exposure. One male exhibited kidney cysts.

At 1000 mg/m^3, facial scabbing and red material around the nose was noted on one male rat starting

on day 14 and continuing until study termination. Five male rats experienced facial scabbing on one or more days during the study. On day six, one male experienced labored respiration at 1-hour post-exposure. Food consumption decreased for the male rats (↓13.3%). Urinalysis results indicated that urobilinogen increased males compared to control (↑250%). Thymus weights were decreased compared to controls for both males and females (↓12.4% and ↓13.1%, respectively). One male exhibited kidney cysts. Individual male animals had incidences of swollen spleen, thickened urinary bladder, and distended ureter. Two males exhibited a dilated pelvis, and one male exhibited an aberrant prostate. Microscopy revealed two males exhibited hyperplasia in the axillary lymph nodes compared to none in the controls. Three of ten males exhibited hemorrhaging in the thymus compared to one in ten in the control.

The systemic LOAEL is 500 mg/m^3 (0.50 mg/L analytical concentration), based upon kidney histopathological changes (appearance of kidney cysts). The systemic NOAEL is 100 mg/m^3 (0.10 mg/L analytical concentration).

The portal of entry LOAEL is 500 mg/m^3 (0.50 mg/L analytical concentration), based upon clinical signs (facial scabbing and red material around the nose in multiple animals, and labored breathing in one animal). The portal of entry NOAEL is 100 mg/m^3 (0.10 mg/L analytical concentration).

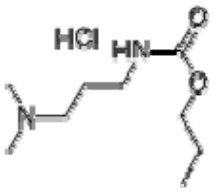
This subchronic inhalation toxicity study in the rats is acceptable/guideline and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided. Quality Assurance statements were not included. A Flagging statement was provided regarding the criteria of 40 CFR 158.34/40 CFR 161.34 for potential adverse effects to the study signed on August 11, 2014, stating that the study neither meets not exceeds any of the applicable criteria.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Propamacarb hydrochloride

Description:	Colorless liquid
Lot/Batch #:	EK1C000648
Purity:	70.1% (w/w active ingredient)
Compound stability:	Stored at room temperature (10 to 30ºC) (stable until expiration date of November 29, 2015)
CAS # of TGAI:	25606-41-1
Structure:	

2. Vehicle: Humidified filtered air

3. Test animals

Species:	Rat
Strain:	Sprague-Dawley
Age/weight at study initiation:	Approximately 7 weeks old; 222 – 321 g males, 149 - 207 g females
Source:	Charles River Laboratories, Inc., Raleigh, NC
Housing:	1 rat/suspended, stainless steel, wire-mesh cage
Diet:	Basal diet Certified Rodent LabDiet® 5002 (meal) (PMI Nutrition International, LLC), *ad libitum* except during exposure.
Water:	Reverse osmosis-treated drinking water, *ad libitum* except during exposure.
Environmental conditions:	**Temperature:** 20.9 to 22.0 C (actual) **Humidity:** 31.1 to 41.1% (actual) **Air changes:** 10 air changes/hour **Photoperiod** 12 hours light/dark
Acclimation period:	Minimum 22 days; before commencement of dosing, animals were acclimated to nose-only exposure tubes for approximately 5 days, gradually increasing periods of restraint time up to the maximum expected duration of 6 hours on fifth day.

B. STUDY DESIGN:

1. In life dates: Start: December 30, 2013; End: May 5, 2014

2. Animal assignment and treatment: Animals were assigned to the test groups noted in Table 1 and were selected for use by a computerized randomization procedure based on body weight stratification in a block design (individual body weights were within ±20% of the mean for each sex). Each group consisted of 10 males and 10 females. The animals were approximately 7 weeks old at the initiation of test substance exposures.

TABLE 1: Study Design for 28 Day Inhalation in Rats after Treatment with Propamocarb Hydrochloride

Test group	Target conc. (mg/m^3)	Target conc. (mg/L) [a]	Analytical conc. (mg/ m^3)	Analytical conc. (mg/L) [a]	MMAD µm	GSD	Rats/sex
Control	0	0.00	0	0	0	0	10
Low (LCT)	100	0.10	99 ± 4.1	0.099	1.3	1.79	10
Mid (MCT)	500	0.50	486 ± 66.2	0.486	1.4	1.78	10
High (HCT)	1000	1.00	1011 ± 100.3	1.011	1.7	2.28	10

[a]Data were converted from mg/m^3 to mg/L by the reviewer dividing by 1000.

3. Dose selection rationale: Not provided.

4. Generation of the test atmosphere / chamber description:

Test atmosphere concentration: Liquid droplet aerosols of the test substance were generated using a modified Inspiron nebulizer. Because of excessive foaming of the test substance during compressed air-powered jet nebulization, each nebulizer was modified by adding a ¼- inch bulkhead fitting and ¼-inch polyethylene tubing to the base of the nebulizer. The fitting and polyethylene tubing allowed foamed test substance to drain from the nebulizer to a reservoir to settle. Once the foamed test substance had settled, it was pumped back into the nebulizer and reused.

For 1000 mg/m^3 treatment groups, facility compressed air was supplied to the nebulizer and was controlled using a regulator. Aerosol from the nebulizer was delivered to conventional nose-only system (CNOS) 4 through a ½-inch T-fitting where it was mixed with humidified supply air to achieve desired concentration. Humidified supply air flow was controlled using rotameter-type flowmeter. Exposure atmosphere was exhausted from the bottom of the CNOS through a Solberg canister type filter system.

Exposure atmosphere for 100 and 500 mg/m^3 groups were derived from a single aerosol generation system. Facility compressed air was supplied to the nebulizer and was controlled using a regulator. Aerosol from the nebulizer was delivered to a mixing plenum prior to being delivered to both exposure systems by positive pressure. Test substance aerosol flow from mixing plenum was controlled using indicating ball or needle valves. Exhaust airflow from the mixing plenum was controlled to equilibrate mixing plenum pressure. Positive plenum pressure was measured using a pressure gauge. Test substance aerosol was delivered to a ½-inch T-fitting prior to entering CNOS 2 and 3 where it was mixed with humidified supply air to achieve desired concentrations. Exposure atmosphere was exhausted from the bottom of each CNOS through a Solberg canister type system. A HPM-1000 aerosol monitor was connected to CNOS 2 and CNOS 3 during exposures. The data displayed by the aerosol monitors was used by laboratory personnel to adjust and maintain exposure concentrations for Groups 2 and 3.

For the control group, humidified supply air was delivered to the exposure system using a rotameter-type flowmeter. A HEPA filter and an activated charcoal bed were used to pre-

treat the supply air prior to delivery to the CNOS.

Results are in table 1 above.

Particle size determination: Aerosol particles size measurements were conducted using a 7-stage stainless-steel cascade impactor (model no. 02-140, IN-TOX Products, Moriarty, NM). Pre-weighed, 22-mm stainless-steel collection substrates were used. Samples were collected at approximately 1.8 LPM for 5, 5, and 1 minute(s) for Exposure System 2, 3, and 4 respectively. The collection substrates were re-weighed and the particles size was calculated based on the impactor state cut-offs. The aerosol particles size was expressed as the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD). Aerosol particles size was collected twice weekly during the study for each test substance exposure concentration.

Results are in Table 1 above.

Inhalation Exposure System Description: Exposures were conducted using 7.9-L stainless steel, conventional nose-only exposure systems with synthetic rubber grommets in exposure ports to engage animal holding tubes. One exposure system was dedicated to each group for the duration of the study. All exposure systems were operated under dynamic conditions with airflow rates based on the compressed air requirements for the aerosol generation and the dilution or supply airflow, and provided sufficient airflow for the number of animals to be exposed. Negative pressure was verified at an open "T"-fitting, in-line between each exposure system and the facility exhaust. Exposure system exhaust passed through the facility exhaust system, which consists of HEPA- and charcoal-filtration.

Exposure system temperature and relative humidity were monitored using and Omega® humidity and temperature transmitter probe. Temperature and relative humidity within each exposure system were continually monitored and recorded at approximately 60-minute intervals. The mean temperature and relative humidity during the animal exposure period were to be 19 C to 25 C and 30% to 70%, respectively. Each nose-only exposure system was operated under dynamic conditions. Airflow rates were manually recorded at approximately 60-minute intervals and were calculated using values from calibrated pressure regulators and/or rotameter-type flowmeters.

5. **Statistics:** Each mean was presented with the standard deviation (SD), standard error (SE) and the number of animals (N) used to calculate the mean. Due to the use of significant figures and the different rounding conventions inherent in the types of software used, the means and SD on the summary and individual tables may differ slightly. Therefore, the use of reported individual values to calculate subsequent parameters or means will, in some instances, yield minor variations from those listed in the report data tables.
   All statistical tests were performed using WTDMS™ unless otherwise noted. Analyses were conducted using two-tailed tests (except as noted otherwise) for minimum significance levels of 1% and 5%, comparing each test substance-treated group to the control group by sex.
   Body weight, body weight change, food consumption, clinical pathology, and organ weight data were subjected to a parametric one-way ANOVA (Snedecor and Cochran, 1980) to determine intergroup differences. If the ANOVA revealed statistically significant ($p<0.05$) intergroup variance, Dunnett's test (Dunnett, 1964) was used to compare the test substance-treated groups to the control group.

The review considers the statistical analysis to be appropriate.

C. METHODS:

1. Observations:

1a. Cageside observations: Animals were observed twice daily for mortality and moribundity.

1b. Clinical examinations: Clinical examinations were conducted daily, prior to exposure, and approximately 0-1 hour (+0.25 h) following the end of exposure (1 h post-exposure). On non-exposure days, animals were observed once daily. Detailed physical examinations were conducted on all animals within 4 days of receipt, the week prior to randomization (± 2 days), on the day of randomization, on the first day of exposure, weekly (± 1 day) during the study period, and on the day of the schedule necropsy.

2. **Body weight:** Animals were weighed and recorded within 4 days of receipt, the week prior to randomization (± 2 days), on the day of randomization, on the first day of exposure, weekly (± 1 day) during the study period, and on the day prior to the scheduled necropsy (non-fasted). Final body weights (fasted) were recorded on the day of the scheduled necropsy.

3. **Food consumption:** Individual food weights were recorded the week prior to randomization (± 2 days), on the day of randomization, weekly (± 1 day) during the study period, and on the day prior to the necropsy (Day 28). Food consumption was determined as g food/kg body weight/day for corresponding body weight intervals.

4. **Ophthalmoscopic examination:** Eyes were examined macroscopically at necropsy on all animals.

5. **Hematology and clinical chemistry:** Blood was collected from all animals at necropsy (Day 28). The animals were fasted overnight prior to blood collection. Blood was collected for coagulation parameters at the time of euthanasia via the vena cava of animals anesthetized by inhalation of isoflurane. Blood was collected into tubes containing K_3EDTA (hematology), sodium citrate (coagulation), or no anticoagulant (clinical/serum chemistry).
The CHECKED (X) parameters were examined.

a. Hematology:

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
X	Blood clotting measurements*		OTHER
X	(Thromboplastin time)	X	Mean platelet volume (MPV)
	(Clotting time)	X	Red cell distribution width (RDW)/morphology
X	(Prothrombin time)	X	Hemoglobin distribution width

* Recommended for subchronic inhalation studies based on Guideline 870.3465

b. Clinical/Serum chemistry:

X	ELECTROLYTES	X	OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphorus	X	Total Cholesterol*
X	Potassium*	X	Globulins
X	Sodium*	X	Glucose*
X	**ENZYMES** (more than 2 hepatic enzymes eg., *)	X	Total bilirubin
X	Alkaline phosphatase*	X	Total serum protein (TP)*
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)	X	Albumin/globulin ratio
X	Alanine aminotransferase (ALT/also SGPT)*	X	Appearance
X	Aspartate aminotransferase (AST/also SGOT)*		
X	Sorbitol dehydrogenase*		
X	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for subchronic inhalation studies based on Guideline 870.3465

6. Urinalysis: Urine was collected from (fasted) animals at the scheduled necropsy (day 28). The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
X	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood / blood cells*
X	Sediment (microscopic)	X	Nitrate
X	Protein*	X	Urobilinogen

* Optional for inhalation toxicity studies

7. Sacrifice and pathology: All animals were sacrificed at study termination and were subjected to macroscopic examination. The CHECKED (X) tissues were collected for histological examination in the chart below. Microscopic examination was performed on tissues from the control and high-concentration group animals as well as any gross lesions from any animal as appropriate. Of the recommended tissues for rat, the bile duct was excluded from examination. The (XX) organs, in addition, were weighed.

X	DIGESTIVE SYSTEM
X	Tongue
X	Salivary glands*
X	Esophagus*
X	Stomach*
X	Duodenum*
X	Jejunum*
X	Ileum*
X	Cecum*
X	Colon*
X	Rectum*
XX	Liver*+
	Gall bladder* (not rat)
	Bile duct* (rat)
X	Pancreas*

X	RESPIRATORY
X	Trachea*
XX	Lung*
X	Nose*
X	Pharynx*
X	Larynx*

X	CARDIOVASC./HEMAT.
X	Aorta, thoracic*
XX	Heart*+
X	Bone marrow*
X	Lymph nodes*
XX	Spleen*+
XX	Thymus*+

X	UROGENITAL
XX	Kidneys*+
X	Urinary bladder*
XX	Testes*+
XX	Epididymides*+
X	Prostate*
X	Seminal vesicles*
XX	Ovaries*+
XX	Uterus*+
X	Mammary gland*

X	NEUROLOGIC
XX	Brain*+
X	Peripheral nerve*
X	Spinal cord (3 levels)*
X	Pituitary*
X	Eyes (optic nerve)*

X	GLANDULAR
XX	Adrenal gland*+
X	Lacrimal gland
X	Parathyroid*
X	Thyroid*

X	OTHER
X	Bone (sternum and/or femur)
X	Skeletal muscle
X	Skin
X	All gross lesions and masses*
X	Cervix
X	Harderian glands
X	Peyer's patches
X	Vagina

* Recommended for subchronic rodent studies based on Guideline 870.3465
\+ Organ weights required

II. RESULTS:

A. OBSERVATIONS :

1. **Clinical signs of toxicity:** Clinical observations that were noted including facial scabbing on facial area or red material around the nose. Of the males treated with 500 mg/m^3, one male experienced both scabbing on facial area and red material around the nose from days 17-28, and two males had red material around their nose on day 25 only. Of the males treated with 1000 mg/m^3, one male experienced both facial scabbing and red material around the nose from days 14-28, and four males had facial scabbing and red material around the nose at one or more observation days, but not through to study termination.

   It was noted by the investigator that labored respiration was observed at the 1-hour post-exposure observation time point in a single 500 mg/m^3 group female on study Day 5 and in a single 1000 mg/m^3 group male on study Day 6. The raw data for these findings was not included in the study report.

2. **Mortality:** All animals survived until scheduled termination.

B. BODY WEIGHT AND WEIGHT GAIN: A summary of mean absolute body weights and body weight gains for each dose group is presented in Table 2. Propamocarb hydrochloride treatment resulted in minor (< 10%) decreased absolute body weights in the 1000 mg/m^3 group males beginning on Day 7 and continuing through Day 27. There were no treatment-related effect on absolute body weights observed in the 100 and 500 mg/m^3 male group. No significant body weight changes were noted in any of the female treatment groups.

TABLE 2. Average Body Weights and Body Weight Gains in Rats Administered Propamocarb Hydrochloride for 28 Days

Analytical concentration (mg/m^3)	Body weights (g ± SD)						Total weight gain	
	-7/-8 days	Day 0	Day 7	Day 14	Day 21	Day 27	g (D 0 to D 27)	% from control
Male								
0	223 ± 17	275 ± 23	316 ± 28.7	353 ± 33	385 ± 36.5	414 ± 38.2	139	0
100	226 ± 18	277 ± 24	318 ± 26.1	354 ± 30	385 ± 35.8	412 ± 37.6	135	↓2.9
500	222 ± 15.7	275 ± 23.3	315 ± 26.1	350 ± 29.4	383 ± 34.3	411 ± 36.6	136	↓2.2
1000	223 ± 11.3	275 ± 20.2	309 ± 27.5	340 ± 30.1	366 ± 34.0	389 ± 37.5	114	↓18
Female								
0	153 ± 12.7	178 ± 19.1	199 ± 17.6	214 ± 20.2	227 ± 20.8	238 ± 23.9	60	0
100	153 ± 9.3	179 ± 14.4	196 ± 13.2	212 ± 15.8	223 ± 14.9	232 ± 16	53	↓11.7
500	154 ± 9.9	180 ± 13.1	195 ± 14.9	210 ± 17.6	223 ± 18.6	231 ± 19.5	51	↓15
1000	154 ± 9.4	178 ± 13.5	194 ± 15.5	209 ± 17.3	223 ± 21.5	232 ± 22.9	54	↓10

Data obtained from pages 61-72 in the study report.
* Statistically different ($p<0.05$) from the control.

C. FOOD CONSUMPTION:

1. Food consumption: There were no effects of treatment on food consumption. It was noted that decreased mean food consumption in the 1000 mg/m^3 group males was observed beginning during study Days 0-7 and persisting for the remainder of the exposure period. The lower food consumption values were consistent with the test substance-related lower body weight gains and/or body weight losses noted in the group during the same intervals.

Table 3. Food consumption (g/rat/day) in Rats Administered Propamocarb Hydrochloride for 28 Days

Interval	Dose Level ((g/animal/day ± SD)			
	0 mg/m^3	100 mg/m^3	500 mg/m^3	1000 mg/m^3
Males				
Day 0-7	26 ± 2.9	26 ± 2.0	26 ± 2.1	25 ± 2.6 (↓3.8%)
Day 7-14	28 ± 2.8	27 ± 2.4	26 ± 2.4	26 ± 2.4 (↓7.1%)
Day 14-21	28 ± 2.7	27 ± 2.6	27 ± 2.4	26 ± 2.4 (↓7.1%)
Day 21-27	29 ± 2.5	28 ± 2.6	27 ± 2.3	26 * ± 2.6 (↓13.3%)
Females				
Day 0-7	19 ± 2.6	17 ± 1.3	18 ± 1.6	18 ± 1.8
Day 7-14	19 ± 2.1	18 * ± 1.0 (↓5.3%)	17 * ± 1.5 (↓10.5%)	18 ± 1.5
Day 14-21	20 ± 1.9	18 ± 2.0	18 ± 1.4	19 ± 2.2
Day 21-27	20 ± 2.2	18 ± 1.9	18 ± 1.2	20 ± 1.8

Data obtained from pages 73-74 in the study report.
* Statistically different from the control group at 0.05 using Dunnett's test

D. OPHTHALMOSCOPIC EXAMINATION:

E. BLOOD ANALYSES:

1. Hematology and Coagulation: Changes in hematological parameters are listed in Table 4. In general, some cell-types showed trends for treatment-related changes, particularly the immune response-related cell types (neutrophils, monocytes and eosinophils). Overall due to variability in measurements, conclusive treatment related effects were not clear. Both neutrophil and monocyte values fell outside of the standard deviation ranges reported in the Charles River CD® IGS Data for Crl:CD(SD) rats* (the same facility that supplied the eats to the Investigator). For many parameters, any treatment-related trends were less clear and statistical significance was not attained (See reviewer comments).

TABLE 4. Hematological and Coagulation Changes in Rats after 28 Days of Treatment with Propamocarb Hydrochloride

Parameter	Males				Females			
	Mean Summary ± SD							
	Dose (mg/m^3)				Dose (mg/m^3)			
	0	100	500	1000	0	100	500	1000
NEU (%)	12.6±4.4	12.8±4.1	15.1±4.3 (↑19.8%)	17.4±9.3 (↑27.6%)	11.4±4.7	11.7±2.9	11.9±4.0	12.8±5.9 (↑12.3%)
NEU ABS (thous/uL)	1.29±0.4	1.36±0.4 (↑5.4%)	1.59±0.5 (↑23.3%)	1.95±1.2 (↑51.2%)	0.85±0.3	0.95±0.2 (↑11.8%)	0.83±0.4	0.96±0.3 (↑12.9%)
LYMPH (%)	82.8±4.9	83.1±4.4	80.6±4.1	77.8±10.4 (↓6.0%)	84.7±5.0	83.6±3.7	83.7±5.4	83.3±5.8

LYMPH ABS (thous/uL)	8.87±3.3	9.01±2.1	8.68±2.3	8.68±2.3	6.48±1.3	6.93±1.2 (↑6.9%)	5.88±2.1 (↓9.3%)	6.60±2.0
MONO (%)	2.7±1.0	2.2±0.7 (↓18.5%)	2.4±1.1 (↓11.1%)	2.9±1.3 (↑7.4%)	1.9±0.5	1.8±0.9 (↓5.3%)	1.9±0.5	1.8±0.5 (↓5.3%)
MONO ABS (thous/uL)	0.27±0.1	0.24±0.1 (↓11.1%)	0.25±0.1 (↓7.4%)	0.32±0.2 (↑18.5%)	0.14±0.0	0.15±0.1 (↑7.1%)	0.14±0.1	0.15±0.1 (↑7.1%)
EOS (%)	1.0±0.4	0.9±0.3 (↓10.0%)	1.1±0.4 (↑10.0%)	0.9±0.3 (↓10.0%)	1.2±0.4	2.2*±1.1 (↑83.3%)	1.9±1.2 (↑58.3%)	1.3±0.5 (↑8.3)
EOS ABS (thous/uL)	0.10±0.04	0.10±0.04	0.11±0.03 (↑10.0%)	0.09±0.03 (↓10.0%)	0.09±0.02	0.18*±0.09 (↑100.0%)	0.14±0.1 (↑55.6%)	0.10±0.04 (↑11.1%)
BASO (%)	0.2±0.1	0.2±0.1	0.2±0.04	0.2±0.04	0.2±0.1	0.2±0.1	0.1±0.1 (↓50.0%)	0.2±0.1

Data obtained from pages 75 to 88 in the study report
* Statistically different from the control group, p>0.05 using Dunnett's test
** Statistically different from the control group, p>0.01 using Dunnett's test

2. Clinical/Serum chemistry: Similar to the hematological parameters, numerous values for the serum chemistry measurements were highly variable and standard deviation values overlapped between dose levels. For some parameters, treatment-related trends were less clear and statistical significance was not attained (Data not shown). None of the minor changes in clinical chemical parameters, were not corroborated with histopathology.

F. URINALYSIS: Among the urine quantitative parameters, a statistically significant increase (p>0.05 using Dunnett's test) in urobilinogen (↑250%) was reported for the male 1000 mg/m^3 group.

G. SACRIFICE AND PATHOLOGY:

1. Organ weight: Table 5 details findings for lung weights and noted changes in other organ weights. There were no treatment-related changes in lung weights at any dose. At 1000 mg/m^3, both sexes exhibited lower absolute thymus weights compared to controls (↓12.4% for males and ↓13.1% for females). Females in the 1000 mg/m^3 treatment group exhibited evident decreases in uterine weight (↓28.6%).

TABLE 5. Organ Weight Changes in Rats after 28 Days of Treatment with Propamocarb Hydrochloride

Parameter	MALES				Females			
	(Mean Summary) Grams ± SD							
	Dose (mg/m^3)				Dose (mg/m^3)			
	0	100	500	1000	0	100	500	1000
Lungs	1.43 ± 0.1	1.40 ± 0.2	1.44 ± 0.1	1.45 ± 0.2	1.14 ± 0.1	1.09 ± 0.1	1.09 ± 0.1	1.07 ± 0.1
Thymus (Absolute)	0.522±0.1	0.502±0.1	0.517±0.1	0.457±0.1 (↓12.4%)	0.432±0.1	0.394±0.1 (↓9.0%)	0.402±0.1 (↓7.1%)	0.376±0.06 (↓13.1%)
Uterus (Absolute)	NA	NA	NA	NA	0.63±0.2	0.62±0.3	0.59±0.2	0.45±0.07 (↓28.6%)

Data obtained from pages 102-119 in the study report.

2. Gross pathology: Macroscopic assessments reported that there were no remarkable lesions found in the lung for either sex and for all dose levels. Kidney cysts were observed in 10% (1/10) of male rats in both the 500 and 1000 mg/m^3 treatment groups. For the male 1000 mg/m^3 group, 20% (2/10) of the animals exhibited a dilated pelvis. Macroscopic findings in the prostate were reported for the male 1000 mg/m^3 treatment group. Specifically, 10% (1/10)

of the rats exhibited adhesions, discoloration, and firm and enlarged prostate. Additionally, 10% (1/10) male rats from the 1000 mg/m^3 treatment group exhibited a swollen spleen, distended ureters, and thickened urinary bladder.

3. **Microscopic pathology:** Table 6 details selected histological findings. Microscopic analysis reported that there were no remarkable lesions found in the lung, nasal cavity (divided into 6 sections), or bronchial lymph nodes for either sex at any dose level. Treatment related microscopic findings were noted in the axillary lymph nodes and the thymus of male rats from the 1000 mg/m^3 group. Two rats exhibited hyperplasia in the axillary lymph nodes compared to none in the control group. Three rats exhibited hemorrhages in the thymus compared to one rat from the control group.

Table 6. Histopathological Changes in Rats after 28 Days of Treatment with Propamocarb Hydrochloride

Target Exposure Concentration (mg/m^3):	Males				Females			
	0	**100**	**500**	**1000**	**0**	**100**	**500**	**1000**
Axillary Lymph Node[a]	10	NA	NA	10	10	NA	NA	10
Hyperplasia	0	-	-	2	0	-	-	0
Thymus[a]	10	NA	1	10	10	1	1	10
Hemorrhage	1	-	1	3	2	1	1	0

Data obtained from pages 120-145 in the study report.
[a]Number of tissues examined from each group.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

Exposure of Crl:CD(SD) rats to propamocarb hydrochloride via nose-only inhalation for 6 hours per day on a 5-day per week basis for 4 weeks at exposure concentrations of 0, 100, 500, and 1000 mg/m^3 was well tolerated. All animals survived until scheduled necropsy without clinical signs of physiologic dysfunction or physical impairment. Non-adverse test substance-related lower body weights and food consumption were noted in 1000 mg/m^3 group males. Therefore, the no-observed-effect concentration (NOEC) was 500 mg/m^3 and the no-observed-adverse-effect concentration (NOAEC) was 1000 mg/m^3, the highest concentration tested.

B. REVIEWER COMMENTS:

The reviewers do not agree with the suggested NOAC determined by the Investigator based on observations in the treated male rat groups. Although all animals survived to the necropsy and there were no adverse effects on body weight for either sex, important clinical effects were observed in animals at the mid- and high-dose groups. The effects and results in this subchronic inhalation toxicity study are as follows:

All animals survived to the scheduled necropsy. There were no treatment related effects on the lung or the nasal passage at any dose tested. There were no treatment-related effects on body weight for either sex, at any dose. At 100 mg/m^3, there were numerous changes in hematological and clinical chemical parameters observed in the absence of clinical signs, organ weight changes, macro- or microscopic changes, which showed no dose response, and were thus considered adaptive. Throughout the study at all doses, some hematological parameters fell outside of the registrant's historical control range.

At 500 mg/m^3, clinical examinations found facial scabbing and red material around the nose in one male starting on study Day 17 and continuing until study termination. Two males were noted with facial scabbing and red material around the nose on study Day 25 only. On Day five, one female experienced labored respiration at 1-hour post-exposure. One male exhibited kidney cysts.

At 1000 mg/m^3, facial scabbing and red material around the nose was noted on one male rat starting on day 14 and continuing until study termination. Five male rats experienced facial scabbing on one or more days during the study. On day six, one male experienced labored respiration at 1-hour post-exposure. Food consumption decreased for the male rats (↓13.3%). Urinalysis results indicated that urobilinogen increased males compared to control (↑250%). Thymus weights were decreased compared to controls for both males and females (↓12.4% and ↓13.1%, respectively). One male exhibited kidney cysts. Individual male animals had incidences of swollen spleen, thickened urinary bladder, and distended ureter. Two males exhibited a dilated pelvis, and one male exhibited an aberrant prostate. Microscopy revealed two males exhibited hyperplasia in the axillary lymph nodes compared to none in the controls. Three of ten males exhibited hemorrhaging in the thymus compared to one in ten in the control.

The systemic LOAEL is 500 mg/m^3 (0.50 mg/L analytical concentration), based upon kidney histopathological changes (appearance of kidney cysts). The systemic NOAEL is 100 mg/m^3 (0.10 mg/L analytical concentration).

The portal of entry LOAEL is 500 mg/m^3 (0.50 mg/L analytical concentration), based upon clinical signs (facial scabbing and red material around the nose in multiple animals, and

labored breathing in one animal). The portal of entry NOAEL is 100 mg/m^3 (0.10 mg/L analytical concentration).

This subchronic inhalation toxicity study in the rats is acceptable/guideline and satisfies the guideline requirement for a subchronic inhalation study OPPTS 870.3465.

C. STUDY DEFICIENCIES:

Major Deficiency:

- The standard deviations for several parameters were highly variable causing the value ranges between dose groups to overlap. For some parameters, treatment-related trends are less clear and statistical significance was not attained. This high variability hampered the proper assessment of biological significance even when dose-related mean values appeared to represent biological trends.

Minor Deficiency:

- The study did not include a rational for the dose selection implemented in the study. Regardless, this deficiency did not compromise the study and the selected range met the criteria required by the guideline OPPTS 870.3465.

*Charles River, CD IGS Rat Technical Resources, CD IGS Rat Model Information Sheet, accesses on 10/28/2014, http://www.criver.com/files/pdfs/rms/cd/rm_rm_d_cd_rat.aspx